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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,933	BOOKSER ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an RCE and amendments filed on 5/27/03. Applicants have amended claim 34. All pending claims were previously rejected. There are thirty-six claims pending and thirty-five under consideration. Claims 1-6 and 8-33 are compound claims. Claims 34-36 are use claims. This is the third action on the merits. The application concerns some phenyl phosphonate compounds and uses thereof.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/27/03 has been entered.

Response to Amendment

3. Applicants' amendment to claim 33 listing the specific diseases to be treated overcomes the indefiniteness rejection made in point #9 of the final rejection. This also overcomes the enablement rejection raised in point #11.

4. The declaration of Dr. Erion under 37 CFR 1.132 filed 5/27/03 is insufficient to overcome the rejection of claims 1-6 and 8-36 based upon indefiniteness and lack of enablement as set forth in the last Office action because:

the declaration contains no new data or references supporting Applicants assertions. The points in sections 4, 5, and 7-10 contain no data but rather only allegations of Applicant. Mere allegations are not probative. *In re CHILOWSKY*, 134 USPQ 515, "[i]n this respect they are not only expressions of opinion but incompetent expressions. We have been unable to find in the facts which the affidavits support a basis for deciding that Chilowsky has complied with the requirements of section 112", *In re LINDELL*, 155 USPQ 521.

In point #6, Dr. Erion offers an opinion based on the data published in Shaw (Pharm. Res.). Shaw (Pharm. Res.) describes experiments correlating results from *in vitro* assay using half-life determinations of eight compounds in dog intestinal homogenate and the pharacokinetics of the eight compounds after oral dosing in dogs. This is not persuasive for three reasons. Nowhere in the present specification is any *in vitro* assay in dog intestinal homogenate disclosed. Have any of Applicants' prodrugs of the compounds of formula (I) even been tested in this protocol? As discussed below in the enablement rejection, the two *in vivo* assays used by Applicants in support of prodrug enablement appear prophetic and have nothing to do with the experiments described in Shaw (Pharm. Res.). Secondly, it is unclear that compounds 2-9 of the reference are properly called prodrugs. The AUC is the total amount of drug effectively delivered to the serum

of the dogs by any particular compound after oral dosing. The AUC of compounds 2-9 is only 16-31% of the amount delivered by the parent active ingredient compound 1, when compound 1 is administered alone. The peak concentrations of the active substance are only 3-17% of that achieved when compound 1 is administered alone. This would not appear to be a therapeutically effective amount. Thirdly, there is a ten-fold variation of the measured half-life of the eight compounds **2-9** *in vitro* in dog intestinal homogenate. Yet there is less than a two-fold variation in terminal half-life for the same compounds when tested *in vivo*. Compound **5** has one of the two shortest measured half-lives *in vitro*. Yet compound 5 has the fourth longest half-life measured *in vivo*. Correlation between *in vitro* and *in vivo* half-lives in this study would appear to be poor.

In point #8 of the declaration, Dr. Erion points to pages 98-108, asserting that passage describes how to make the prodrugs of formula I. In fact, that passage appears to describe the synthesis of compounds of formula I, not prodrugs of the compounds of formula I.

Election/Restrictions

5. This application contains claim 7 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicants' request to the Examiner to cancel claim 7 is noted. Unfortunately, the Examiner has no such ability, especially after a traversed restriction requirement. Such a request should be made in the amendments section of Applicants' response.

6. Objection is made to claims 1-6, 8-29, and 31-36 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula I(b) contains compounds drawn to the non-elected inventions with X other than carbon. Formula I(a) is drawn to non-elected inventions.

Applicants made no traversal of this objection.

Title

7. After the restriction, the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The Examiner suggests replacing the phrase "Novel Aryl" with "Phenyl Phosphonate".

Priority

8. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1, 2, 4-6, 8-11, and 14-36 of this application. Applicants' present formula (I) is far broader

than the formula (I) of 60/187,750. For example, presently L can be a linking phenyl group. In the provisional application the cyclic linking group was limited to seven specific heteroaryl rings but not phenyl. Thus, the effective filing date of these claims is 3/7/01.

Claim Rejections - 35 USC § 112

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-6, 8-17, 19, 26, 30, and 34-36 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). the term "alicyclic" in claim 1 is used by the claim to mean "alicyclic, saturated heterocyclic, and aromatic", while the accepted meaning is "any aliphatic compound that contains a ring of carbon atoms", BioTech's Life Science Dictionary, copyright 1995-98. The Condensed Chemical Dictionary defines the term as "... carbon atoms in closed ring structures". An alicyclic ring may contain

multiple bonds but may not be aromatic and may not contain any heteroatoms." The term is indefinite because the specification does not clearly redefine the term.

Applicants make four arguments. Firstly, they correctly assert that case law indicates they may be their own lexicographers. Secondly, they point to lines 17-21, page 5 for the definition of "alicyclic". Thirdly, they quote further from the MPEP §2173.05(a). Fourthly, they point to a paper in the scientific journal JOC to show that piperidine, piperazine, and morpholine are called, by the Spanish authors of the paper, "secondary alicyclic amines".

This is not persuasive. According to new USPTO policy, the basis of this rejection has changed from whether the definition used by Applicants is repugnant to the skilled organic chemist, which was at issue in *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947), to the presently used analysis as to if the disputed term is clearly redefined. As discussed in the next point, "alicyclic" is not clearly redefined by Applicants. Secondly, lines 17-21, page 5 use open language "includes" and "but is not limited to". What other structures are included in their definition? Lines 17-21, page 5 fail to clearly redefine the term. Thirdly, Applicants' themselves fail to quote the most recent version of last paragraph of MPEP §2173.05(a) in its' entirety,

> "TERMS USED CONTRARY TO THEIR ORDINARY MEANING MUST BE CLEARLY REDEFINED IN THE WRITTEN

> DESCRIPTION Consistent with the well-established axiom in patent law that a patentee or applicant is free to be his or her own lexicographer, a patentee or applicant may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings if the written description clearly redefines the terms. See, e.g., *Process Control Corp. v. HydReclaim Corp.,* 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999) ("While we have held many times that a patentee can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning," in such a situation the written description must clearly redefine a claim term "so as to put a reasonable competitor or one reasonably skilled in the art on notice that the patentee intended to so redefine that claim term."); *Hormone Research Foundation Inc. v. Genentech Inc.,* 904 F.2d 1558, 15 USPQ2d 1039 (Fed. Cir. 1990). Accordingly, when there is more than one definition for a term, it is incumbent upon applicant to make clear which definition is being relied upon to claim the invention. Until the meaning of a term or phrase used in a claim is clear, a rejection under 35 U.S.C. 112, second paragraph is appropriate. It is appropriate to compare the meaning of terms given in technical dictionaries in order to ascertain the accepted meaning of a term in the art. *In re Barr*, 444 F.2d 588, 170 USPQ 330 (CCPA 1971)."

Applicants fail to make clear how they intend to redefine the standard chemical term "alicyclic". Fourthly, piperidine, which contains a single secondary amino nitrogen atom, is called by the Spanish authors of the JOC paper, a "secondary alicyclic amine". It is hard to see how such usage would indicate that "alicyclic" by itself, without the modifiers "secondary" and "amine" used in the JOC paper would be understood by the average chemist to include piperidine. The Examiner cited a dictionary in the previous office action in accordance with *In re Barr*, 444

F.2d 588, 170 USPQ 330. How does the isolated usage in a single paper by a non-native speaker of English indicate that this dictionary definition is incorrect?

10. Claims 1-6 and 8-36 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "pharmaceutically acceptable prodrugs ... thereof" occurs near the end of claim 1. The phrase "prodrugs thereof" is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' prodrugs are molecules whose structure lays outside the subject matter of formula I, but upon metabolism in the body are converted to active compounds falling within the structural scope of formula I. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. In the discussion of enablement of prodrug, the Examiner cites references showing the lack of recognition in the art of medicinal chemistry of what structurally constitutes a prodrug.

The Examiner suggests deleting the word prodrug.

Applicants make five arguments. Firstly, they assert that prodrug development is routine. Secondly that the open language used in the specification to describe the structures of their claimed prodrugs is permitted. Thirdly, the specification contains adequate definitions of "acyl" and "aryl", which in turn, were used in the definition of prodrug. Fourthly that the meaning of prodrug is both clear and art-recognized. Fifthly, that prodrug is a limitation used in a number of issued US Patents. Only the third point is persuasive.

To the first point, assertion is not evidence and the question of the routine nature of prodrug discovery is an enablement issue, not an issue of the structures of Applicants' claimed compounds. The question is not whether such compounds may be found but rather if the average organic chemist can envision the structures of the claimed derivatives from the single word prodrug. While open language is routine in patent specifications, when it is used to change the meaning of a standard term, then a clear definition is required. To the forth point, in the present case there is dispute as to the meaning of the concept of prodrug as well as to the structures implied by the term. The American Heritage® Dictionary of the English Language: Fourth Edition, 2000 defines prodrug as "An inactive precursor of a drug, converted into its active form in the body by normal metabolic processes". This is a different meaning than used by Applicants. Applicants elsewhere argue

that the metabolic process used to establish whether any compound is a prodrug can be done *in vitro* rather than "in the body". Do Applicants believe that a prodrug itself must be biologically inactive? However, even if the dispute as to the concept of prodrug is resolved, that will not resolve the question of the structures of the claimed prodrugs, which is the heart of this rejection.

As to the fifth point, the indefiniteness remains despite what was allowed in another case. The U.S. Court of Customs and Patent Appeals wrote *In re Giolito* 188 USPQ 645: "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others. See *In re Margaroli,* 50 CCPA 1400, 318 F.2d 348, 138 USPQ 158 (1963); *In re Wright*, 45 CCPA 1005, 256 F.2d 583, 118 USPQ 287 (1958); *In re Launder*, 41 CCPA 887, 212 F.2d 603, 101 USPQ 391 (1954)".

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 8-36 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Applicants are not enabled for using prodrugs. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large degree of experimentation.

b) The direction concerning the prodrugs is found in The guidance concerning the prodrugs in the specification is found in formulas VI-VIII in pages 30-31, in the synthesis passage beginning at line 20, page 100, and more specifically in the passage spanning line 11, page 11 to line 26, page 15. Formulas VI-VIII are embraced by formula (I) and do not provide guidance to the structures of those out that scope. The passage beginning at line 20, page 100 is labeled synthesis of prodrugs but in fact, outlines synthesis of formula (I) and does not provide any guidance to the structures of those out that scope. There are nine types of prodrugs disclosed in the passage spanning line 11, page 11 to line 26, page 15. Most are covered by formula (I) but Formula B, page 11, the right side of Formula E, page 13, Formulas E1, E-2, E3-, and F, page 14, the trichloroethyl ester in the last paragraph on page 15 are outside the scope of formula (I) and constitute the only guidance in the specification as to which compounds, not embraced by formula (I), are prodrugs of formula (I).

c) Examples 17 and 18, page 130-131, lack any chemical data characterizing the products, and fail to specify the staring materials used, stating only an "aminoacid ester" is to be used. The two examples give no biological data and do not offer any evidence whether the products of these reactions are or are not prodrugs. Thus, these are prophetic, not working examples. In addition, as

discussed above, these do not bear on the question of compounds lying outside the scope of formula (I). In Example I, spanning pages 138-139, Applicants describe a protocol for determining if a compound is a prodrug in rats. There are no results reported and it appears to be a prophetic example. It is unclear if any of the compounds lying outside the scope of formula (I) have been tested in this protocol. In Example N, spanning pages 140-141, Applicants describe a second protocol for determining if a compound is a prodrug in rats. There are no results reported and it is unclear if any of the compounds lying outside the scope of formula (I) have been tested in this protocol. Thus, Applicants have provided no working examples of a prodrug. d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states

that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Sanchez (J. Med. Chem.) in the four sentences spanning page 1766 implies that the prodrug nature of an alanate ester was only found empirically after the compound was made. Serafinowska (J. Med. Chem., Ref CJ) in the last complete paragraph on the left side of page 1375 describes the synthesis of thirty-eight potential prodrug phosphonate esters and two amides. Nineteen of these displayed the measurable bioavailability. Of these, only seven had bioavailability greater than 10% required of a successful prodrug. It appears that only three of these substances were further evaluated as possible prodrugs. Thus, the skill in the art of synthesis of prodrugs would appear low and not predictable as of 1995.

Bundgaard (J. Med. Chem.) in the second sentence states that a major problem exists in prodrug design, namely designing the proper derivative. The second paragraph makes the point that some ethyl ester prodrugs are hydrolyzed *in vivo* and some are not. Thus, establishing the lack of predictability in the prodrug area as of 1987. Banker (Modern Pharmaceutics) says on page 451, first paragraph that "preparation of prodrugs is becoming a common practice", implying that it is not routine as of 1996. Banker (Modern Pharmaceutics) says on page 596, third paragraph that "extensive development must be undertaken to find the correct chemical modification". Clearly an invitation to open-ended, potentially inconclusive, and unpredictable research.

Wolff (Medicinal Chemistry) in second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success of preparing prodrugs. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard protocol discussed in the last sentence of this paragraph is particularly relevant. Finally, concerning the amine containing drugs, Shan (J. Pharmaceutical Sci.) indicates in the first paragraph, page 765 that "[a]pplying similar strategies to the preparation of prodrugs of amine-containing drugs is somewhat more problematic ... because of the stability of the amide bond". Thus

indicating that the research program outlined above may be inconclusive when applied to drugs that are amines.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 1.

Thus, undue experimentation will be required to determine if any particular derivative of formula I is, in fact, a prodrug.

Applicants argue that working examples are not required for enablement, Applicants assert that the experimentation to develop a prodrug is routine, and thirdly, point to the advanced age of the references used by the Examiner is his analysis of the state of the art. Firstly, as discussed above lack of working examples, which Applicants admit to be the case in the present application, is one of eight factors to be used in reaching a conclusion concerning enablement and any conclusion as to whether the experimentation required is undue. Secondly, whether undue experimentation is required is a conclusion to be reached after an analysis of the facts. It itself, is not a fact to be disputed or simply asserted. Applicants themselves address only two of the eight factors used to reach such a conclusion. Thirdly, three of the references used by the Examiner were kindly supplied by the Applicants to bolster their argument for enablement. These three

are Sanchez (J. Med. Chem.), Serafinowska (J. Med. Chem., Ref CJ), and Bundgaard (J. Med. Chem.). Presumably Applicants thought they did accurately describe the state of the art when they supplied them to the Examiner. If Applicants have more up to date references concerning the state of the art of prodrug discovery, then such references would be a welcome addition to the facts used as one of the eight factors required by *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the absence of such up to date material, the age of the Examiners references does not invalidate them.

12. Claims 1-6 and 8-36 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention. Applicants are not enabled for making prodrugs of the compounds of formula (I). Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must be even more unclear. Directions to a team of synthetic pharmaceutical chemists and

metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

13. Claims 1-6 and 8-36 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase "pharmaceutically acceptable prodrugs ... thereof" describes the function of the claimed derivatives but provides no structural guidance to the average medicinal chemist indicating that the average medicinal chemist would recognize that the applicant had possession of the claimed invention. According to the MPEP § 2163 I,

> "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc., 525* U.S. 55, 68, 119 S. Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai*

> *Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). "Compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed. '" I, 296 F.3d at 1324, 63 USPQ2d at 1613."

What are the chemical formulas of the claimed prodrugs?

Further quoting from the MPEP § 2163 I "A question as to whether a specification provides an adequate written description may arise in the context of an original claim which is not described sufficiently (see, e.g., *Enzo Biochem*, 296 F.3d at 1329, 63 USPQ2d at 1616 (Fed. Cir. 2002); *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398)". "However, as discussed in paragraph I., *supra*, the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its

function." In the present case, Applicants have even failed to provide us with a method of preparing the claimed prodrugs, merely with a description of what they are suppose to do. Where is the evidence of the correlation between the function "prodrug" and the structure of the derivates that provide that function?

14. Claim 36 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of diabetes, does not reasonably provide enablement for treatment of "glycogen storage diseases" generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants have not demonstrated nor have they alleged there is any correlation between the *in vitro* assay, whose results are described in Table 3, page 133, and clinical efficacy against any specific disease. Case law is clear on this point. In an unpredictable art, such as diabetes pharmacology, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

Applicants have clarified that "glycogen storage diseases" are the enzyme deficiency disorders of seven specific types of glycogenosis (Cori classification) as further described in Chen (Principles of Internal Medicine). The Table 347-1 on page 2178 of Chen (Principles of Internal Medicine) teaches that none of these

diseases involves fructose-1,6-bisphosphaaste. The only glycogen storage disease involving fructose is type VII, Tarui disease. This disease is caused by a deficiency of the phosphofructokinase enzyme. The Figure 347-1 on page 2177 makes clear that this is a different enzyme than fructose-1,6-bisphosphaaste. Why do Applicants believe that their fructose-1,6-bisphosphaaste inhibitors will be beneficiation for any of these enzyme disorders? It is not logical that an inhibitor of fructose-1,6-bisphosphaaste would be beneficial in a disease caused by a deficiency of this very enzyme.

Applicants argue that any compound which inhibits glycogen accumulation in the body would necessarily be effective in the treatment of the claimed "glycogen storage diseases". This is neither true nor on point. Applicants do not address the issues discussed in the preceding paragraph. Unless the mechanism of action of Applicants' compounds has some bearing upon the disease process, even if it inhibits glycogen storage by another mechanism, then it cannot affect the disease process. Six of the seven specific types of glycogenosis (Cori classification) have nothing to due with Applicants mechanism of action. The seventh type would be exacerbated, not improved by a compound acting by Applicants' mechanism. In any case, the standard is the correlation of the assays

used to the claimed disease. The standard is not whether Applicants compounds could hypothetically have such an action.

15. Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The two provisos in the next to last three lines of claim 1 lack description. Nowhere in the specification is such a relationship linking the description among radical R^5 and radicals J^2-J^6 described. Such a negative limitation requires description. In *Ex parte Grasselli, et al.* 231 USPQ 393, decided June 30, 1983, the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences said: "we agree with the examiner's position of record that the negative limitations recited in the present claims, which did not appear in the specification as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112." "It might be added that the express exclusion of certain elements implies the permissible inclusion of all other elements not so expressly excluded. This clearly illustrates that such negative limitations do, in fact, introduce new concepts."

Applicants argue that that removal of elements from a Markush list of claim limitations is a permitted practice. Secondly, they attempt top factually distinguish their proviso from *Ex parte Grasselli, et al.* 231 USPQ 393, stating that no Markush list was present in *Ex parte Grasselli, et al.* 231 USPQ 393. This is not persuasive.

Applicants did not remove any elements from the Markush lists describing radical R^5 and radicals J^2-J^6. What they did was exclude two specific species by creating a new relationship among these radicals. Until the Examiner made the anticipation rejection, the Applicant had no reason to single out the species embraced by the proviso. When filed, the application did not recognize that species as special, nor is the Applicant now claiming that he recognized it as so. Applicants are invited to remove items from the lists describing radical R^5 and radicals J^2-J^6.

Since Applicants did not, in fact, remove items from a Markush list, the issue of whether *Ex parte Grasselli, et al.* 231 USPQ 393 removed such items need not be considered.

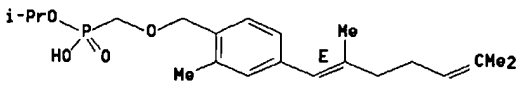
Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

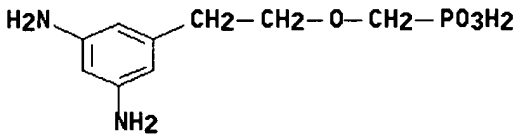
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Biller ('153). There is one compound taught in this reference that fit formula (I) with one $R^1Y = {}^{i}PrO$, R^1 = isopropyl, the other R^1Y = HO, R^1 = hydrogen, L = the alkyleneoxyalkylene group $-CH_2-O-CH_2-$, R^5 = disubstituted phenyl, J^2 = methyl, and J^4 = 2,6-dimethyl-1,5-heptadienyl. It has Registry Number 151070-53-0 is shown below. The compound is found in lines 46-61, column 34. Applicants' proviso 10) on page 5 of the recent set of pending claims excludes compounds with R^1 = alkyl when the other is hydrogen. However, the compound shown below may well be a prodrug of the compound with both R^1 = hydrogen. That compound is not excluded by the proviso. The compound with R^1 = hydrogen is the basis of the rejection.

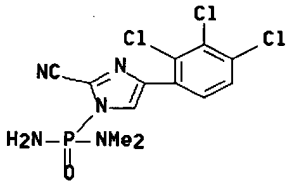


17. Claims 1-3, 8, 9, 11, 14-17, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Krecmerova (Collection of Czechoslovak Chemical Communications). There is one compound taught in this reference that fit formula (I) with both R^1Y = HO, R^1 = hydrogen, L = the alkyleneoxyalkylene group -CH_2-O-CH_2-CH_2-, R^5 = disubstituted phenyl, J^3 = J^5 = amino. It has Registry Number 168837-87-4 and is shown below. The compound is found in the reference in the formula on page 662 and is structure **XVIII**. Synthesis is taught in the paragraph spanning pages 667-668.



18. Claims 1, 2, 8, 14-17, 19, and 20 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Buss ('557). There is one compound taught in this reference that fit formula (I) with both R^1Y = $MeNR^6$, R^1 = R^6 = methyl, R^1 = R^6 = hydrogen, L = -1,4-imidazoyl-, R^5 = trisubstituted phenyl, J^2 = J^3 = J^4 = chlorine. The compound is found in the Table in column 9, as entry 39. Applicants' proviso 6) and proviso 10) on page 5 of the recent set of pending claims excludes compounds with R^1 = alkyl when the other is hydrogen. However, the compound shown below may well be a prodrug

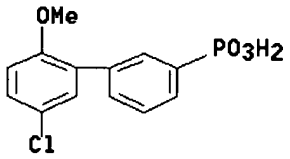
of the compound with both R^1Y = HO. That compound is not excluded by the proviso. The compound shown below may well be a prodrug of the compound with one R^1Y = HO and the other $R^1Y = NH_2$. That compound is also not excluded by the proviso. When Applicant claims a compound in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. *In re Best*, 195 USPQ 430.



19. Claims 1, 2, 8, 14-17, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated, in the alternative, under 35 U.S.C. 103(a) as obvious over Huang (Synthesis). There is one compound taught in this reference that fit formula (I) with both R^1Y = EtO, R^1 = ethyl, L = -1,4-imidazoyl-, R^5 = disubstituted phenyl, J^3 = J^4 = methyl. The compound is found in the Table in page 511, as entry **2e**. Applicants' proviso 10) on page 5 of the recent set of pending claims excludes compounds with both R^1 = alkyl. However, the compound described may well be a prodrug of the compound with both R^1Y = HO. That compound is not excluded

by the proviso. When Applicant claims a compound in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. *In re Best*, 195 USPQ 430.

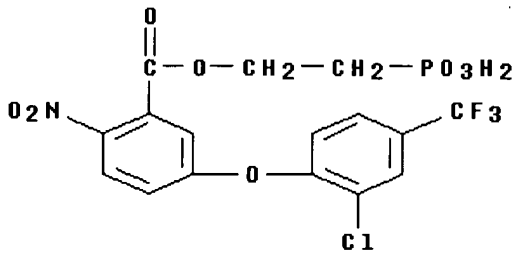
20. Claims 1, 2, 8-11, 14, 15, 17, 20, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Duffy (WO 2001089457 A2). There are four compounds taught in this reference that fit formula (I). The one shown below has both R^1Y = HO, R^1 = hydrogen, L = -1,3-phenyl-, R^5 = disubstituted phenyl, J^2 = methoxyl, R^{11} = methyl, and J^5 = chlorine. It has Registry Number 118847-92-0 and is found in the reference in line 19, page 26. The other compounds are in line 5, page 25, line 24, page 25, and line 5, page 26.



Conclusion

21. Claims 1, 2, 8, 9, 11, 12, 14, 15, 17, 20, and 29 are novel over Diel ('701) because Applicants' provisos, discussed above, formally overcome this rejection. Those provisos are new matter. There are two compounds taught in this reference that fit formula (I), one of which is shown below. It has both R^1Y = HO, L = the

alkyleneoxycarbonyl group $-CH_2-CH_2-O-C(O)-$, R^5 = disubstituted phenyl, J_2 = nitro, $J^4 = OR^2$, with R^2 = the substituted aryl group phenyl, where the substituents are the halo group chlorine and the perhaloalkyl group CF_3. Line 3, page 5 of the specification discloses that all aryl groups may be substituted. The halo group and the perhaloalkyl group are disclosed as permissible substituents in line 26 and line 30 of page 5. The compounds are found in the reference in Table I, column 9 and are compounds 1.03 and 1.16.



22. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any

inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie
Patent Examiner
Art Unit 1624

TCMcK